50. (Amended) The method according to claim 49, wherein the immunoprotective gene is a gene whose product at least partially inhibits expression of [the] an MHC [proteins] protein or antigen presentation.

51. (Amended) The method according to claim 43, wherein the immunoprotective gene is selected from the group consisting of a gene for gp19k of adenovirus, [the] an ICP47 gene of herpes virus, and [the] a UL18 gene of cytomegalovirus.

B5 concl'd

REMARKS

Claims 26-56 are pending in this application. Claims 27, 28, 31-33, 45, 46, and 49-51 have been amended in the instant amendment to more particularly point out and distinctly claim that which Applicants consider their invention. Support for amended claims 27, 28, 31-33, 45, 46, and 49-51 is found within the claims as originally filed and in the Specification. No new matter has been added. All of the claims under consideration, as amended, are presented as an Appendix attached hereto.

Summary of the Examiner's Office Action

The Office Action dated June 9, 1999 contains the following issues requiring a response:

(1) Species Election Requirement Under Section 121; and
(2) Claims 26-56 Under Section 103(a) as being allegedly unpatentable over Leibowitz *et al.*, in view of Linsley *et al.*, and Marshall.

Each of the issues raised by the Examiner is discussed below. Applicants believe that the foregoing amendment and the following remarks respond completely to the objections and rejections. Applicants further believe the claims are in condition for allowance.

(1) Species Election Requirement Under Section 121

On page 2 of the Office Action, the Examiner contends that claims 26-56 are generic to a plurality of disclosed distinct species comprising an

immunosuppressive agent and an immunoprotective gene. The Examiner requires election of a single species under 35 U.S.C. 121, wherein the species comprises one specific immunosuppressive agent and one specific immunoprotective gene as recited in generic claims 27, 28, 33, 45, 46, and 51. During a telephone conversation between Applicants' attorney Ross J. Oehler and the Examiner on May 14, 1999, Applicants provisionally elected 1) a monoclonal or polyclonal antibody within claims 27 and 45, with traverse, 2) a CTLA4Ig antibody within claims 28 and 46, with traverse, and 3) a gp19k of adenovirus immunoprotective gene within claims 33 and 51, with traverse. Applicants herein affirm this species election, with traverse. Pending claims 26-56 read upon Applicants' provisionally elected species. Applicants submit that the species of the invention are drawn to a single inventive concept, and are properly considered together.

Under 35 U.S.C. § 121, restriction may be required if "two or more independent and distinct inventions are claimed in one application." However, even with patentably distinct inventions, restriction is not required unless one of the following reasons appear (MPEP 808.02):

1. Separate classification
2. Separate status in the art; or
3. Different field of search.

The above-cited language of 35 U.S.C. § 121 is clear in that the requirement to restrict an application to one of the inventions disclosed therein is proper only if the disclosed inventions are both independent and distinct. While Applicants take no position on the patentable distinctness of the claimed species, Applicants submit that the species of claims 36-56 are not independent and are so linked as to form a single general inventive concept.

However, even if one accepts the MPEP's interpretation of 35 U.S.C. §121, the mere existence of two or more independent or distinct inventions in one application is not sufficient to justify a restriction requirement. According to the guidelines in MPEP § 803, if the search and examination of an entire application can be made without serious burden, the examiner must examine it on the merits, even though it includes claims to distinct or independent inventions.

In this case, the appropriate standard for restriction is under the unity of invention criteria of the PCT. Applicants submit that, under the requirement for unity of invention, the pending claims relate to one invention or to a group of inventions so linked as to form a single general inventive concept. MPEP §

1850 [citing PCT Article 3(4)(iii) and 17(3)(a), PCT Rule 3.1, and 37 C.F.R. § 1.475]. Unity of invention exists when there is a technical relationship among the claimed inventions involving one or more special technical features, meaning those technical features that define a contribution which each of the inventions considered as a whole, makes over the prior art. MPEP § 1850.

Claims 26-56 Species Are Drawn To A Single Inventive Concept And Share A Special Technical Feature

Applying the appropriate criteria in the instant application, Applicants note that the special technical feature of the claims of the instant application is the combination of an immunosuppressive agent and a recombinant adenovirus whose genome comprises a first recombinant DNA containing a therapeutic gene and a second recombinant DNA containing an immunoprotective gene of generic independent claims 26 and 43. The remaining claims, 27-42 and 44-56, all depend directly or indirectly from generic independent claims 26 and 43. Therefore, all of pending claims 24-56 share the special technical feature of the combination of an immunosuppressive agent and a recombinant adenovirus whose genome comprises a first recombinant DNA containing a therapeutic gene and a second recombinant DNA containing an immunoprotective gene.

Applicants respectfully submit that the species of claims 24-56 are drawn to a single general inventive concept as defined in PCT Rule 13.1, and comprise the same or corresponding special technical features as defined under PCT Rule 13.2. This special technical feature is the combination of an immunosuppressive agent and a recombinant adenovirus whose genome comprises a first recombinant DNA containing a therapeutic gene and a second recombinant DNA containing an immunoprotective gene. Accordingly, the claimed species are linked as to form a single general inventive concept under 37 CFR § 1.475 and PCT Rule 13.1. Accordingly, modification of the Requirement for Species Election and examination of all species of claims 24-56 is believed to be in order and is earnestly requested.

Examination Of Claims 24-56 Species Does Not Present Undue Burden On The Examiner

Applicants respectfully submit that prosecution of all claimed species in the present Application is appropriate. Under Patent Office examining procedures, "[i]f the search and examination of an entire application can be made without serious burden, the Examiner must examine it on the merits, even though it includes claims to distinct or independent inventions" (MPEP 803, Rev. 8, May 1988) (emphasis added). In the Office Action, the Examiner has not even averred that the claimed species fall into different classifications. Applicants submit that the claimed species fail to define products and methods for using such products, with biological properties so distinct as to warrant separate examination and search. The present claimed species represent a web of knowledge and continuity of effort that merits examination in a single application.

Accordingly, all claims are related to the combination of an immunosuppressive agent and a recombinant adenovirus whose genome comprises a first recombinant DNA containing a therapeutic gene and a second recombinant DNA containing an immunoprotective gene of generic independent claims 26 (a composition comprising such a combination) and 43 (a method for expressing a therapeutic gene comprising using such a combination). Thus, all of these claims involve a fundamental determination of the novelty of the combination of an immunosuppressive agent and a recombinant adenovirus whose genome comprises a first recombinant DNA containing a therapeutic gene and a second recombinant DNA containing an immunoprotective gene. To the extent that this determination would be made, it is submitted that a preponderantly coextensive search would result. In particular, an exhaustive search for the immunosuppressive agents and immunoprotective genes of independent claims 26 and 43 would encompass the art disclosing the specific claimed species of claims 27, 28, 33, 45, 46, and 51. Similarly, a search for the species as recited in claims 27, 28, 33, 45, 46, and 51 would reveal information about the combination of an immunosuppressive agent and a recombinant adenovirus whose genome comprises a first recombinant DNA containing a therapeutic gene and a second recombinant DNA containing an immunoprotective gene. Indeed, performing the entire search covering the combination of an immunosuppressive agent and a recombinant adenovirus whose genome comprises a first recombinant DNA containing a therapeutic

gene and a second recombinant DNA containing an immunoprotective gene and its species and uses is less burdensome on the Examiner than separate searches, which necessarily involve duplication of searching efforts.

Thus, Applicants submit that the search and examination of the entire Application can be made without serious burden. Applicants respectfully submit that conjoint examination and inclusion of all species of the claims of the present Application would not present an undue burden on the Examiner and, accordingly, withdrawal of the Requirement for Election of Species is believed to be in order. In the event that the species election requirement is maintained, Applicants reserve the right to file Divisional Applications directed to the subject matter of the non-elected species.

(2) Rejection of Claims 26-56 Under Section 103(a) as being allegedly unpatentable over Leibowitz *et al.*, in view of Linsley *et al.*, and Marshall.

Claims 26-56 stand rejected under Section 103(a) as being allegedly unpatentable over Leibowitz *et al.*, in view of Linsley *et al.*, and Marshall. Applicants have amended claims 27, 28, 31-33, 45, 46, and 49-51 and claims 26-56 are pending in the instant amendment.

Applicants respectfully traverse this rejection with respect to the remaining claims. The combination of references in no way teaches or suggests Applicants' invention and, therefore, fails to establish a *prima facie* case of obviousness. Accordingly, Applicants request respectfully that the rejection be reconsidered and withdrawn.

(a) Discussion of the cited references

Leibowitz *et al.*

Leibowitz *et al.* are concerned with methods to decrease a transplant recipient's immune response to a donor cell to treat a genetic disorder, a wound, a burn, or a disease. Specifically, this reference teaches methods of treating donor cells intended for transplantation with adenoviral E19 protein to reduce transplant rejection of the introduced donor cell by the recipient's immune system (see pages 2-3). The Examples disclosed by Leibowitz *et al.* teach the use of retroviral vector transfer of adenoviral E19 protein into keratinocytes, pancreatic β-islet cells, and cardiac cells.

Leibowitz *et al.* do not teach a composition comprising an immunosuppressive agent and a recombinant adenovirus whose genome comprises a first recombinant DNA containing a therapeutic gene and a second recombinant DNA containing an immunoprotective gene. Furthermore, these authors do not teach methods for expressing a therapeutic gene comprising administering an immunosuppressive agent and a recombinant adenovirus whose genome comprises a first recombinant DNA containing a therapeutic gene and a second recombinant DNA containing an immunoprotective gene.

Linsley *et al.*

Linsley *et al.* present an *in vivo* study of immunosuppression using CTLA4Ig. This reference teaches that CTLA4Ig is a soluble form of the extracellular domain of the T cell surface molecule CTLA-4 (Abstract). These authors teach that CTLA4Ig binds to the B7 molecule on the surface of antigen presenting cells with high avidity (Abstract). In addition, Linsley *et al.* teach that human CTLA4Ig binds to murine B7 and inhibits murine T cell responses *in vitro* and *in vivo* (see page 792, third column and Figures 2-5).

Linsley *et al.* fails to teach that CTLA4Ig would sufficiently block a host immune response to adenoviral infection. Linsley *et al.* certainly do not teach a composition comprising an immunosuppressive agent and a recombinant adenovirus whose genome comprises a first recombinant DNA containing a therapeutic gene and a second recombinant DNA containing an immunoprotective gene. Furthermore, these authors do not teach methods for expressing a therapeutic gene comprising administering an immunosuppressive agent and a recombinant adenovirus whose genome comprises a first recombinant DNA containing a therapeutic gene and a second recombinant DNA containing an immunoprotective gene.

Marshall

The Marshall reference was published in the August 25, 1995 issue of *Science*. In the instant amendment, Applicants set forth that the subject matter of the present application is entitled to the benefit of foreign priority under 35 U.S.C. § 119(a) of French Patent Application No. FR95/01662, filed February 14, 1995. Thus, with a foreign priority date of February 14, 1995, Marshall, 1995 is not available as prior art to the instant application. Applicants are in the process of obtaining a certified copy of the French Patent Application No.

FR95/01662, filed February 14, 1995. Applicants will submit this certified copy as soon as it is available.

Furthermore, even if the Marshall reference was available, there is not hint or suggestion contained in this reference to make and use Applicants' claimed invention. Marshall presents a brief review of gene therapy efforts directed to treatment of cystic fibrosis. Marshall teaches that crippled adenoviruses are relied upon in CF gene therapy clinical trials because of their tropism for the lungs and their ability to penetrate non-dividing cells (see page 1052, column 2). In addition, Marshall teaches the advantages and disadvantages of a variety of gene therapy vectors (see Table on page 1053). Marshall teaches that a drawback of adenovirus is that it expresses proteins that trigger immune responses (page 1052, column 2 and Table).

Marshall does not teach how to overcome this drawback of adenovirus. Specifically, Marshall fails to teach a composition comprising an immunosuppressive agent and a recombinant adenovirus whose genome comprises a first recombinant DNA containing a therapeutic gene and a second recombinant DNA containing an immunoprotective gene. Furthermore, Marshall does not teach methods for expressing a therapeutic gene comprising administering an immunosuppressive agent and a recombinant adenovirus whose genome comprises a first recombinant DNA containing a therapeutic gene and a second recombinant DNA containing an immunoprotective gene.

(b) Leibowitz *et al.* Do Not Render Obvious the Invention of Claims

Applicants' independent claims 26 and 43 define a composition comprising an immunosuppressive agent and a recombinant adenovirus whose genome comprises a first recombinant DNA containing a therapeutic gene and a second recombinant DNA containing an immunoprotective gene (claim 26) and a method for expressing a therapeutic gene comprising administering an immunosuppressive agent and a recombinant adenovirus whose genome comprises a first recombinant DNA containing a therapeutic gene and a second recombinant DNA containing an immunoprotective gene (claim 43). The reference cited by the Examiner does not teach or suggest the invention defined by independent claims 26 and 43. The reference is deficient because it:

(1) discloses only methods of treating donor cells intended for transplantation with adenoviral E19 protein

to reduce transplant rejection of the introduced donor cell by the recipient's immune system; and
(2) fails to enable the immunoprotective activity of observed by Applicants in Example 2 of the Specification.

Leibowitz *et al.* does not teach the combination of an immunosuppressive agent and a recombinant adenovirus whose genome comprises a first recombinant DNA containing a therapeutic gene and a second recombinant DNA containing an immunoprotective gene. Absent such a disclosure, Leibowitz *et al.* cannot possibly render *prima facie* obvious the invention defined by Applicants' independent claims 26 and 43, or the claims dependent thereon.

(c) Linsley *et al.* and Marshall do not correct the deficiencies of Leibowitz *et al.*

Neither Linsley *et al.* nor Marshall disclose Applicants' claimed invention. As stated above, Linsley *et al.* teach that human CTLA4Ig binds to murine B7 and inhibits murine T cell responses *in vitro* and *in vivo*. Marshall teaches that a drawback of adenovirus is the immune reaction it induces upon infection of a host. These references fail to teach or motivate one of ordinary skill in the art to combine their teachings with that of Leibowitz *et al.* to obtain Applicant's claimed invention. Nothing in the art cited by the Examiner teaches combination of an immunosuppressive agent and a recombinant adenovirus whose genome comprises a first recombinant DNA containing a therapeutic gene and a second recombinant DNA containing an immunoprotective gene in a composition (independent claim 26) or in a method for expressing a therapeutic gene (Independent claim 43). Applicants were the first to make this unexpected discovery.

(d) The cited references fail to enable Applicants claimed invention

As discussed above, none of the prior art cited by the Examiner teach Applicants' claimed invention. The proper standard is whether the prior art would have suggested to one of ordinary skill in the art that the invention should be carried out and would have a reasonable likelihood of success, viewed in

light of the prior art. *In re Dow Chemical Company*, 5 USPQ 2d 1529, 1531 (Federal Circuit, 1988).

> Both the suggestion and the expectation of success must be founded in the prior art, not in Applicants' disclosure. Id.

In this case the cited combination of references simply does not suggest to one of ordinary skill in the art that Applicants' claimed invention could be achieved with a reasonable likelihood of success.

As stated above, the combination of Leibowitz *et al.* with Linsley *et al.* and Marshall fails to teach or motivate the skilled artisan to combine an immunosuppressive agent and a recombinant adenovirus whose genome comprises a first recombinant DNA containing a therapeutic gene and a second recombinant DNA containing an immunoprotective gene in a composition (independent claim 26) or in a method for expressing a therapeutic gene (Independent claim 43). These cited references certainly fail to provide the artisan with the expectation of success.

(e) The rejection is based on improper hindsight

As discussed above, none of the references relied upon teach or suggest the claimed invention. Accordingly, the rejection must be based on improper hindsight given the benefit of Applicants' disclosure. However, use of hindsight reconstruction of an invention using Applicant's teachings is clearly improper.

In this case, nothing in the art cited by the Examiner teaches or suggests the combination of an immunosuppressive agent and a recombinant adenovirus whose genome comprises a first recombinant DNA containing a therapeutic gene and a second recombinant DNA containing an immunoprotective gene in a composition (independent claim 26) or in a method for expressing a therapeutic gene (Independent claim 43). Therefore, this rejection must be based on improper hindsight given the benefit of Applicants' disclosure.

(f) Applicants have demonstrated an unexpected result

Applicants have demonstrated that combined *in vivo* administration of an immunosuppressive agent and an adenovirus comprising a therapeutic gene and an immunoprotective gene induces prolonged therapeutic gene expression (see Example 2). This prolongation of gene expression is markedly greater than

that which could have been expected from the simple juxtaposition of the respective effects of an immunosuppressant and a recombinant adenovirus comprising a therapeutic gene and an immunoprotective gene. Nothing in the art cited by the Examiner teaches or suggests the extent of therapeutic gene expression demonstrated by Applicants. Accordingly, Applicants' results can only be regarded as surprising and unexpected.

(g) Summary

Applicants submit respectfully that

1- Leibowitz *et al.* does not teach or suggest the claimed invention;
2- Linsley *et al.* and Marshall fail to remedy the inherent deficiencies of Leibowitz *et al.*;
3- the Marshall reference is not available as prior art;
4- Applicants have demonstrated a surprising and unexpected result; and
5- the rejection is based on an improper hindsight standard.

Accordingly, Applicants submit that the combination of Leibowitz *et al.* with Linsley *et al.* and Marshall fails to establish a *prima facie* case of obviousness. However, assuming *arguendo* a *prima facie* case may be made, Applicants have established a surprising and unexpected result of prolonged therapeutic gene expression. Therefore, Applicants request respectfully that the rejection be reconsidered and withdrawn.

Conclusion

In view of the foregoing amendments and remarks, Applicants submit that this application is in condition for allowance. Favorable reconsideration and an action passing this case to issue are therefore requested respectfully. If a telephone interview would be of assistance in advancing prosecution of this application, Applicant's agent invites the Examiner to contact her at the number provided below.

Respectfully submitted,

Dated: December 7, 1999

Rachel H. Rondinelli, Ph.D.
Agent for Applicants
Registration No. 45,052

Rhône-Poulenc Rorer Inc.
P.O. Box 5093, Mail Drop 3C43
Collegeville, PA 19426-0997
Telephone: (610) 454-3178
Facsimile: (610) 454-3808

APPENDIX
U.S. Patent Application Serial No. 08/894,246
"Medicinal Combination Useful For *In Vivo* Exogenic Transfection and Expression"
RPR File No. EX95001-US
Pending Claims

26. A composition comprising an immunosuppressive agent and a recombinant adenovirus whose genome comprises a first recombinant DNA containing a therapeutic gene and a second recombinant DNA containing an immunoprotective gene.

27. (Amended) The composition according to claim 26, wherein the immunosuppressive agent is selected from the group consisting of cyclosporin, FK506, azathioprine, corticosteroid, and a monoclonal or a polyclonal antibody that is able to inactivate an immune molecule or induce destruction of an immune cell carrying this molecule.

28. (Amended) The composition according to claim 27, wherein the antibody is selected from the group consisting of anti-CD4, -CD2, -CD3, -CD8, -CD28, -B7, -ICAM-1 and -LFA-1 antibodies, and CTLA4Ig.

29. The composition according to claim 26, wherein the therapeutic gene encodes a therapeutic protein.

30. The composition according to claim 26, wherein the therapeutic gene encodes a therapeutic RNA.

31. (Amended) The composition according to claim 26, wherein the immunoprotective gene is a gene whose product acts on the activity of a major histocompatibility complex (MHC) or on the activity of a cytokine.

32. (Amended) The composition according to claim 31, wherein the immunoprotective gene is a gene whose product at least partially inhibits expression of an MHC protein or antigen presentation.

33. (Amended) The composition according to claim 26, wherein the immunoprotective gene is selected from the group consisting of a gene for gp19k of adenovirus, an ICP47 gene of herpes virus, and a UL18 gene of cytomegalovirus.

34. The composition according to claim 26, wherein the two recombinant DNAs of the adenovirus genome constitute a single transcriptional entity.

35. The composition according to claim 26, wherein the two recombinant DNAs each include an identical transcriptional promoter.

36. The composition according to claim 35, wherein the two recombinant DNAs are inserted in the same orientation.

37. The composition according to claim 26, wherein the two recombinant DNAs are inserted into the same region of the adenovirus genome.

38. The composition according to claim 37, wherein the two recombinant DNAs are inserted within the E1, E3 or E4 regions.

39. The composition according to claim 26, wherein the two recombinant DNAs are inserted into different sites in the adenovirus genome.

40. The composition according to claim 39, wherein one of the recombinant DNAs is inserted within the E1 region and the other within the E3 or E4 region.

41. The composition according to claim 26, wherein the adenovirus is a defective recombinant adenovirus which encompasses the ITR sequences and a sequence permitting encapsidation and which carries a deletion of all or part of the E1 and E4 genes.

42. The composition according to claim 26, wherein the adenovirus concerned is an adenovirus from whose genome all or part of the E1, E3, L5 and E4 genes have been deleted.

43. A method for expression of a therapeutic gene from an adenovirus comprising consecutively or simultaneously administering an immunosuppressive agent and a recombinant adenovirus whose genome comprises a first recombinant DNA containing a therapeutic gene and a second recombinant DNA containing an immunoprotective gene, to a subject.

44. The method according to claim 43, wherein the recombinant adenovirus is administered in vivo.

45. (Amended) The method according to claim 43, wherein the immunosuppressive agent is selected from the group consisting of cyclosporin, FK506, azathioprine, corticosteroid, and a monoclonal or a polyclonal antibody that is able to inactivate an immune molecule or induce destruction of an immune cell carrying this molecule.

46. (Amended) The method according to claim 45, wherein the antibody is selected from the group consisting of anti-CD4, -CD2, -CD3, -CD8, -CD28, -B7, -ICAM-1 and -LFA-1 antibodies, and CTLA4Ig.

47. The method according to claim 43, wherein the therapeutic gene encodes a therapeutic protein.

48. The method according to claim 43, wherein the therapeutic gene encodes a therapeutic RNA.

49. (Amended) The method according to claim 43, wherein the immunoprotective gene is a gene whose product acts on the activity of a major histocompatibility complex (MHC) or on the activity of a cytokine.

50. (Amended) The method according to claim 49, wherein the immunoprotective gene is a gene whose product at least partially inhibits expression of an MHC protein or antigen presentation.

51. (Amended) The method according to claim 43, wherein the immunoprotective gene is selected from the group consisting of a gene for gp19k of adenovirus, an ICP47 gene of herpes virus, and a UL18 gene of cytomegalovirus.

52. The method according to claim 43, wherein the two recombinant DNAs of the adenovirus genome constitute a single transcriptional entity.

53. The method according to claim 43, wherein the two recombinant DNAs each include an identical transcriptional promoter.

54. The method according to claim 53, wherein the two recombinant DNAs are inserted in the same orientation.

55. The method according to claim 43, wherein the immunosuppressive agent is injected both before and after injection of the adenovirus.

56. The method according to claim 43, wherein the immunosuppressive agent and the recombinant adenovirus are injected simultaneously.